Message

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Sent: 2/22/2011 7:22:02 PM
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Subject: NEWS UPDATES: EPA Pilots Highlight Challenges To Adopting New Testing In Risk Analysis (Inside EPA)

EPA Pilots Highlight Challenges To Adopting New Testing In Risk Analysis

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EPA is launching two projects to pilot next generation risk assessments as a way of testing how to incorporate new methods of toxicity testing and molecular systems biology advancements into its risk assessments, but the pilot assessments of ozone and benzene are providing a primer of both the promise and the challenges of the new techniques.

EPA scientists and collaborators unveiled plans for the pilots during a Feb. 15-16 conference in Washington, DC, on the "NexGen" program, which is generally seeking to determine how to incorporate high throughput toxicology screening test methods, molecular systems biology and bioinformatics approaches into its risk assessment practice as recommended by the National Academy of Sciences (NAS) in a landmark 2007 report. The new technology and types of data are challenging because they require a fundamentally different approach to toxicology, the science that underlies risk assessment.

Ila Cote, EPA's NexGen program director, explained that the agency selected benzene and ozone for pilot assessments because there is a wealth of traditional data about each -- providing a counterpoint to the new kinds of data the agency is trying to integrate.

But the group's efforts quickly ran into challenges: some of the types of new data officials wanted to consider were not available for ozone, and so EPA is performing its own study of ozone's effects on human lung function in order to generate it. Benzene has also proven a challenge as the chemical cannot be tested in existing high throughput screening assays that are seen as the backbone of future toxicity testing. Chemicals that are volatile -- like benzene -- or are insoluble in water cannot be tested in the current high throughput screening assays.

One of the key challenges is understanding information from new *in vitro* assays that test chemicals in human cells. These tests eliminate questions of species relevance, but they raise new questions, such as how to understand the results of toxicity tests that do not include metabolism.

Robert Devlin, the EPA scientist leading the ozone study, explained that the study is designed to explore how well *in vitro* assays predict *in vivo* responses in humans. The scientists are exposing 30 volunteers to ozone on two separate occasions. "Markers of lung injury and inflammation are measured," Devlin explained, by removing epithelial cells in the airway and arranging them on a micro-array to determine toxicity pathways. The second part of the study involves taking cells from the same volunteers, and exposing the cells *in vitro* to varying concentrations of ozone, Devlin said. Then, results from the *in vivo* and *in vitro* tests will be compared to determine how well the toxicity pathways identified in the *in vitro* study predicted the effects in the cells exposed *in vivo*.

The goals of the NexGen ozone study include characterizing toxicity pathways -- or the changes in cells caused by exposure to ozone that can eventually lead to a health effect -- both in the cells exposed when the volunteers were breathing the ozone and when their cells alone were exposed to ozone. The project also aims to "Develop models that can assess how accurately the in vitro pathways predict human responses," according to slides that Devlin presented at the conference. *Relevant documents are available on InsideEPA.com.*

"We have virtually completed most of the *in vitro* studies," Devlin said. "*In vivo*, we've exposed seven of the 30 people. We'll probably finish this summer."

Toxicity pathways are both a challenge and a promise of the new approach to toxicity testing. The hope is that once toxicity pathways are understood, testing will be based on upstream gene or cell changes before an actual health effect occurs -- making them more sensitive and predictive of health risks rather than reactive to harms that have already transpired -- such as epidemiology studies. But the *in vitro* approach also requires understanding what all of the myriad toxicity pathways are.

One of the NexGen collaborators, University of Ottawa Professor Daniel Krewski, urged the beginning of a new research program to map and gather understanding of each toxicity pathway. Krewski compared the challenge to that of the human genome project, which over 10 years mapped every gene in the human body. Krewski was also the chairman of the NAS committee that wrote the seminal report urging EPA to begin research on how to adopt the new toxicology testing approaches.

However, some in the audience expressed concerns. Ruthann Rudel, of the Silent Spring Institute, questioned Krewski's premise during a discussion session at the conference. She noted that effects can vary greatly based on the exposure -- how often it happens and in what stage of life or development. "The idea of a discrete and knowable set of toxicity pathways struck me as not realistic," Rudel said. She noted that endocrine pathways depend "entirely" on when exposure to an endocrine disrupting chemical occurs.

Meanwhile, EPA's benzene project has raised other challenges, even though it, like ozone, has a strong database of traditional animal toxicology data. Martyn Smith, a professor at the University of California Berkeley who is leading the benzene project, explained that the chemical would not test positive in many of the existing major tests: it is not cytotoxic, persistent or bioaccumulative, it is negative in the Ames test for mutagenicity -- and yet it is an "established cause of leukemia" and its toxicity was known as early as the turn of the century, Smith said.

He indicates that "*in vitro* methods to predict leukemogens need development," according to slides he presented at the conference. But Smith added that some emerging new data, such as human and animal biomarkers, can be used to examine the dose-response relationship at the low, environmentally relevant levels, and could inform risk assessment. The team is considering how this and other new data -- epidemiological studies, systems biology data, genetic risk factors, lifestage susceptibility and others -- could be applied to traditional toxicology knowledge about benzene to advance understanding of its risks. This new information could "support epidemiology conclusions, explore dose-response, identify susceptible populations and provide information on the effects of co-exposures," Smith said.

In addition to the pilots, the NexGen program is also seeking to create a framework for thinking about how the assessments should be performed. The project considers advice from three sources, Cote and Krewski said, including the NAS' 2009 report on Science and Decisions: Advancing Risk Assessment. The document offers recommendations on how to break deadlock over various issues within assessments. One of the key recommendations applied to the NexGen project, Cote said, is the idea that not all risks

assessments have to be performed in the same way and to the same level of complexity. Cote presented a slide proposing three broad categories of assessments, based on the amount and types of data available about each chemical, as well as the type of risk management decision the assessment supports.

A synopsis of the program explains that EPA's National Center for Environmental Assessment (NCEA), "anticipates implementing a new tiered health assessment paradigm. This new paradigm is aimed at creating health assessments that are more responsive to the needs of program offices, including the ability to accurately assess chemical health risks in a cost effective and more rapid manner." NCEA performs the agency's key Integrated Risk Information System assessments, the basis of many agency rules.

The program is trying to incorporate the new data in part to deal with some of the problems inherent in traditional animal testing, such as relating the results to human health, understanding variability among humans and the limited capacity of such testing approaches compared to the thousands of chemicals on the market for which limited environment, health and safety data is available. Key questions to be addressed through the project, according to Cote, include identifying "specific disease signatures, or pathways"; estimating "relative potencies based on molecular events"; and improving "our understanding of currently problematic issues," including responses at low, environmentally relevant doses, variability between species and between people and exposures to mixtures of stressors.

Participants, however, raised questions about critical aspects of the program during a feedback session at the conference. Pat Casano, an attorney with General Electric Co., questioned the NexGen collaborators about how they will "tackle defining adversity," or what changes seen in *in vitro* tests will be considered harmful effects.

Linda Birnbaum, director of the National Institute of Environmental Health Sciences, replied that "for an individual we can define what is adverse. I'm not sure we can define that for a population." Other members of the NexGen collaboration also indicated this critical point is an ongoing research question.

"I'm wrestling in my own mind with something that causes biological change but is not adverse," said David Dix, an EPA scientist.

And Martin Stephens, of the Humane Society of the U.S., asked whether EPA is "developing exposure methodology alongside the [cellular toxicity tests] so these two fields don't get out of step. Cote noted that the NAS in the past year began a study of new ways to measure and consider exposure science -- a report she said the agency will wait upon before making changes to its existing ways of collecting and analyzing exposure information. -- *Maria Hegstad*

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